# PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

AP

PCT

To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>see form PCT/ISA/220 | Date of mailing<br>*(day/month/year)* see form PCT/ISA/210 (second sheet)<br>**FOR FURTHER ACTION**<br>See paragraph 2 below |
| International application No.<br>PCT/EP2005/050181 | International filing date *(day/month/year)*<br>18.01.2005 |
| Priority date *(day/month/year)*<br>21.01.2004 | |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K9/08, A61K31/496 | |
| Applicant<br>JANSSEN PHARMACEUTICA N.V. | |

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/050181

## Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-13 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 3,11,12 |
| | No: | Claims | 1,2,4-10,13 |
| Industrial applicability (IA) | Yes: | Claims | 1-13 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents are referred to:

D1: WO 96/13499 A

D2: WO 99/55313 A

D3: Atherosclerosis vol. 144 (suppl. 1): Various abstracts on pages 38 and 39 (1999)

Novelty

The subject-matter of present claims 1-13 is considered novel (Article 33(2) PCT), as none of the (oral) solutions disclosed in the prior art anticipates the claimed solution (compare **D1**: example 8, "compound A" can be any of the compounds of the invention, e.g. compound 40; **D2**: page 2, lines 23-27; page 7, lines 10-13; example 3 (compound A is compound 40; see page 19, last par.); **D3**: notably the abstract by Bode et al. on page 38, and the abstract by Dupont et al. on page 39).

Inventive Step

1 - Document **D1** is considered to be the closest state of the art. It discloses apolipoprotein-B synthesis inhibitors (page 1, lines 1-6; claims), e.g. mitratapide (component 40). It suggests pharmaceutical compositions for these compounds, e.g. oral solutions (page 10, lines 9-12 and example 8) and injectable solutions (page 10, lines 18-20; example 11).

The solution of claim 1 differs from the teaching of D1, notably example 8, in that it comprises a pharmaceutically acceptable solvent in which mitratapide has a solubility of 5 mg/ml or higher at a temperature of 22°C, and an antioxidant.

The problem to be solved by claim 1 is to provide a solution for oral administration that is stable, easy to use and meets the requirements regarding antimicrobial efficacy.

The solution of claim 1 cannot be considered inventive, as it is considered to be within the normal competence of the skilled person, to formulate a solution employing (co)solvents in which the active is indeed appreciably soluble, and to find out which solvents could be used for this. In fact, D1 also suggests to use other, non-aqueous, vehicles for oral liquid preparations, e.g. glycols, oily and alcohols (page 10, lines 9-12). Furthermore, it appears that the present application only discloses the advantages of using PEG 400 as a solvent in terms of antimicrobial activity (which is a well-known property of PEGs) and (in

combination with an antioxidant) stability, no advantages of using the other solvents in which mitratapide has a solubility over 5 mg/ml appears to be disclosed. The presence of an antioxidant per se is also considered to be obvious, the present application only presents particular advantages of adding an antioxidant in combination with PEG.
To conclude, starting from D1, the incorporation of any solvent wherein mitratapide has a solubility of at least 5 mg/ml, and an antioxidant in a mitratapide solution cannot be considered inventive, and hence claim 1 is considered to lack an inventive step (Article 33(3) PCT).
2 - Also starting from **D2** and **D3**, which disclose aqueous oral solutions comprising cyclodextrin (see passages cited above and in the search report), no inventive step could be recognised over the full scope of claim 1, as with respect to such formulations the application only appears to present advantageous effects when using PEG as a solvent.
3 - Mutatis mutandis the same arguments apply to independent claim 13, which can also not be seen as inventive (Article 33(3) PCT).
4 - Dependent claims 3, 11 and 12 can be considered inventive over D1-D3 (Article 33(3) PCT), as the combination of PEG 400 and antioxidant is considered non-obvious in view of its effect on stability of mitratapide.
5 - None of the other dependent claims 2 and 4-10 appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step with respect to the prior art named in the present proceedings, as the additional features of the said dependent claims concern minor modifications which lie within the normal practice of the skilled person.

Industrial applicability
Claims 1-13 comply with the requirements of Article 33(4) PCT.